Interview Summary	Application No.	Applicant(s)	
	10/020,882	TOBE, SHELDON	
	Examiner	Art Unit	
	JOHN PAK	1616	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JOHN PAK*. (3)_____.

(2) *NEIL HUGHES*. (4)_____.

Date of Interview: *02 August 2007*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *On 8/2/2007, Mr. Hughes sent a 22 page fax, which contained claim amendments, explanation as to adequate descriptive support, and explanation of regional anti-coagulation treatment. A copy of this fax is attached hereto*.

Claim(s) discussed: *All*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The Examiner and Mr. Hughes discussed several ways of amending the claims in order to expedite prosecution. These initial discussions were conducted on 7/31/2007 and 8/1/2007. On 8/2/2007, Mr. Hughes faxed a proposal, which detailed the changes under discussion and which was accepted by the Examiner on 8/3/2007 with some minor changes, as shown in the attached Examiner's Amendment. Mr. Hughes was asked to provide explanation of descriptive support for claim 26 and explanation for "regional"citrate anti-coagulation therapy .

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

PLEASE DELIVER IMMEDIATELY TO EXAMINER PAK

IN THE UNITED STATES PATENT OFFICE

Application No. 10/020,882

Our Ref: PT-1949001

CUSTOMER NO. 23607

Applicant: Dialysis Solutions Inc.

Agent: Neil H. Hughes, P. Eng.
c/o Ivor M. Hughes
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Patent & Trademark Agents
Suite 200
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Title: STERILE LOW BICARBONATE DIALYSIS CONCENTRATE SOLUTIONS
Examiner: John D. Pak
Group Art Unit: 1616

No. of Pages of Response including this sheet: 21

DELIVERED TO FACSIMILE NO. 1-571-273-0620

Dear Sir:

OFFICIAL COMMUNICATION

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the United States Patent Office Facsimile No. 1-571-273-0620 to the attention of Examiner Pak on the date shown below, including:

1. Proposed Amendments to Claims dated August 2, 2007 ;
2. **Essentials of anticoagulation in hemodialysis by Karl-Georg Fischer of the University Hospital Freiburg Germany**

Signature: _____ Date: August 2, 2007

Neil H. Hughes, P.Eng
Registration No. 33,636
Agent for Applicant

— Part of Interview Summary —

IN THE UNITED STATES PATENT OFFICE

Application No. 10/020,882

Our Reference No. PT-1949001

Applicant: Dialysis Solutions Inc.

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Title: STERILE LOW BICARBONATE DIALYSIS CONCENTRATE SOLUTIONS

Inventors: Sheldon Tobe

Filing Date: December 19, 2001

Art Unit: 1616

Examiner: John D. Pak

Due Date: August 3, 2007

FURTHER PROPOSED AMENDMENTS TO CLAIMS

August 2, 2007

VIA FACSIMILE (1-571-273-0620)

United States Patent and Trademark Office
Customer Service Window, Mail Stop AF
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Dear Examiner Pak:

Applicant respectfully requests that the following amended proposal be considered by the Examiner in order to place this case in condition for allowance.

Part of Interview Summary

IN THE CLAIMS

With this amendment claims 24,26, and 31 to 37 are revised and resubmitted as a proposal for the Examiner's consideration. Claims 31 to 37 are newly provided and cover the subject matter of dependent method and kit claims 2 to 8, 11 and 12 but made dependent on claims 24 and 26 to limit the scope to those claims to the subject matter of claims 24 and 26.

1. (cancelled)

2. (withdrawn) A kit for preparing a dialysis solution comprising the sterile dialysis concentrate composition of claim 1 and optionally instructions for its use.

3. (withdrawn) The kit of claim 2 further comprising sterile water sufficient to dilute the concentrate to a solution comprising Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

4. (withdrawn) A method of preparing a sterile dialysis solution comprising diluting a sterile, dialysis concentrate composition of claim 1 in a sufficient amount of sterile water to prepare a dialysis solution comprising Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

5. (withdrawn) A method for providing continuous renal replacement therapy to a patient comprising administering a sterile dialysis solution prepared according to the method of claim 4 in conjunction with a regional citrate anti-coagulant solution to a patient in need thereof.

6. (withdrawn) A method of preparing a sterile dialysis solution or infusate comprising diluting a sterile, dialysis concentrate composition of claim 1 in a sufficient amount of sterile water to prepare an infusate comprising Na 140±14 mmol/l. Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

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7. (withdrawn) A method for treating acute renal failure in a critically ill patient without introducing calcium into the blood removed from the patient during dialysis comprising administering a sterile dialysis solution prepared according to the method of claim 6 in conjunction with a regional citrate anti-coagulant solution to a patient in need thereof.

8. (withdrawn) A method for providing hemofiltration to a patient comprising administering a sterile infusate prepared according to the method of claim 6 in conjunction with a regional citrate anti-coagulant solution to a patient in need thereof.

9. (cancelled)

10. (cancelled)

11. (withdrawn) A method of preparation of a sterile calcium-free bicarbonate concentrate according to claim 1 as an infusate for hemofiltration.

12. (withdrawn) A method of preparation of a sterile, calcium free bicarbonate concentrate according to claim 1 as a dialysis solution for use in metabolic acidosis.

13. (withdrawn) A method for correcting bicarbonate levels in a patient during dialysis comprising providing a dialysate mixture having a bicarbonate level sufficiently low so as to minimize the risk of metabolic complication in the patient, preferably between 20-30 mmol/litre, wherein should the patient's bicarbonate level drop below the preferred level, bicarbonate diffuses from the dialysate across the semipermable membrane to the patient to correct the problem, and wherein if there is an excess of bicarbonate in the blood of the patient then bicarbonate diffuses from the blood to the dialysate to correct the problem.

14. (cancelled)

15. (withdrawn) A method for treating acute renal failure in a critically ill patient comprising dialyzing blood from the patient, without introducing calcium into the blood removed from the

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patient during dialysis, by using a sterile dialysis solution having a bicarbonate concentration within the range of about 5-30 mmol/litre.

16. (withdrawn) The use of claim 15 wherein the solution further comprises at least one of potassium, glucose, and ketones such as b hydroxy-butyrate.

17. (cancelled)

18. (cancelled)

19. (cancelled)

20. (cancelled)

21. (cancelled)

22. (cancelled)

23. (cancelled)

24. (currently amended) A sterile calcium free low bicarbonate dialysis concentrate composition containing sodium chloride, magnesium chloride and sodium bicarbonate for continuous renal replacement therapy and for use in the preparation of a sterile calcium free dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a the sterile calcium free dialysis solution for continuous renal replacement therapy, ~~further comprising a physiological acceptable diluent and~~ having ion concentrations of Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

25. (Cancelled) ~~A sterile calcium free low bicarbonate dialysis concentrate composition for continuous renal replacement therapy for use in the preparation of a dialysis solution comprising~~

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~~sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a sterile dialysis solution for continuous renal replacement therapy, further comprising a physiologically acceptable diluent and having ion concentrations of Na 140±10% mmol/l, Mg 0.75±10% mmol/l, Cl 116.5 ± 10% mmol/l, and HCO3 25.0 ± 10% mmol/l.~~

26. (currently amended) A sterile calcium free low bicarbonate dialysis concentrate composition containing sodium chloride, magnesium chloride and sodium bicarbonate for continuous renal replacement therapy for use in the preparation of a sterile calcium free dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a the sterile calcium free dialysis solution for continuous renal replacement therapy, ~~further comprising a physiologically acceptable diluent and~~ having ion concentrations of Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 of from 20 to less than 30 mmol/l.

27. (cancelled) ~~A sterile calcium free low bicarbonate dialysis concentrate composition for continuous renal replacement therapy for use in the preparation of a dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a sterile dialysis solution for continuous renal replacement therapy, further comprising a physiologically acceptable diluent and having effective ion concentrations of Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and wherein the HCO3 is provided in an effective concentration consisting essentially of from 20 to less than 30 mmol/l.~~

28. (cancelled) ~~A sterile calcium free low bicarbonate dialysis concentrate composition for continuous renal replacement therapy for use in the preparation of a dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a sterile dialysis solution for continuous renal replacement therapy, further comprising a physiologically acceptable diluent and having effective ion concentrations of Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl~~

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~~116.5 ± 11 mmol/l, and wherein the HCO3 is provided in an effective concentration consisting essentially of 25.0 ± 2.5 mmol/l.~~

29. (cancelled) ~~A sterile calcium free low bicarbonate dialysis concentrate composition for continuous renal replacement therapy for use in the preparation of a dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a sterile dialysis solution for continuous renal replacement therapy, further comprising a physiologically acceptable diluent and having effective ion concentrations of Na 140±10% mmol/l, Mg 0.75±10% mmol/l, Cl 116.5 ± 10% mmol/l, and wherein the HCO3 is provided in an effective concentration consisting essentially of 25.0 ± 10% mmol/l.~~

30. (cancelled) ~~A sterile dialysis solution comprising the concentrate as claimed in any of claims 24 to 30 and a physiologically acceptable diluent.~~

31. (newly presented) A kit for preparing a sterile calcium free dialysis solution comprising the sterile calcium free dialysis concentrate composition of claim 24 or 26 and optionally instructions for its use.

32. (newly presented) The kit of claim 31 further comprising sterile water sufficient to dilute the concentrate to a sterile calcium free dialysis solution comprising Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

33. (newly presented) A method of preparing a sterile calcium free dialysis solution comprising diluting a sterile calcium free dialysis concentrate composition of claim 24 or 26 in a sufficient amount of sterile water to prepare a sterile calcium free dialysis solution comprising Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

34. (newly presented) A method for providing continuous renal replacement therapy to a patient comprising administering a sterile calcium free dialysis solution prepared according to the

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method of claim 33 in conjunction with a regional citrate anti-coagulant solution to a patient in need thereof.

35. (newly presented) A method of preparing a sterile calcium free dialysis solution or infusate comprising diluting a sterile calcium free dialysis concentrate composition of claim 24 or 26 in a sufficient amount of sterile water to prepare an infusate comprising Na 140±14 mmol/l, Mg 0.75±0.07 mmol/l, Cl 116.5 ± 11 mmol/l, and HCO3 25.0 ± 2.5 mmol/l.

36. (newly presented) A method for treating acute renal failure in a critically ill patient without introducing calcium into the blood removed from the patient during dialysis comprising administering a sterile calcium free dialysis solution prepared according to the method of claim 35 in conjunction with a regional citrate anti-coagulant solution to a patient in need thereof.

37. (newly presented) A method for providing hemofiltration to a patient comprising administering a sterile infusate prepared according to the method of claim 35 in conjunction with a regional citrate anti-coagulant solution to a patient in need thereof.

REMARKS

Referring to the Examiner's telephone inquires of July 31, 2007 and August 2, 2007 and in order to expedite this application Applicant has amended the claims consistent with the discussions with Examiner Pak to include the subject matter of pending claims 24 and 26 and the subject matter related to method and kit claims of the same breadth without prejudice to filing a continuation application . All other claims have been cancelled.

Applicant appreciates Examiner's comments and on this basis, Applicant wishes to proceed with amendments to the claim set focusing on the subject matter set out in the amended claim set provided.

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Applicant therefore provides within this proposal amended claims 24, 26 and 31 through 37 which are entirely based on the subject matter of claim 24 while maintaining claim 26 as discussed havng support for the range 20-30 mmol/l on page 7 at line 23 of the application as filed. Further this proposal includes method and kit claims as suggested by the Examiner.. Full consideration is respectfully requested and appreciated.

With respect to the limitation in claim 26 of the range of bicarbonate of 20 to less than 30 mmol/l Applicant submits that this range would be apparent to one skilled in the art in reading the claim in view of the specification and the common knowledge of the art which clearly focuses the invention to bicarbonate levels below 30mmol/l. At page 7 line 23 the range is defined as in the range of preferably between 20 to 30 mmol/l. Full consideration is respectfully requested and appreciated.

With respect to the term "regional" in the dependent claims Applicant attaches an article entitled **Essentials of anticoagulation in hemodialysis by Karl-Georg Fischer of the University Hospital Freiburg Germany** addressing and clarifying the meaning of this term. The term regional focuses therapy regionally instead of systemically. If further clarification is need please advise Applicant.

The Examiner is thanked for his time and consideration of the proposed claim set and a forthcoming notice of allowance is earnestly solicited.

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If any questions arise, the Examiner is respectfully requested to contact Neil Hughes at (905) 771-6414 at the Examiner's convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for the Applicant

NHH/dj

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Hemodialysis International 2007; 11:178–189

Core Curriculum

Essentials of anticoagulation in hemodialysis

Karl-Georg FISCHER

Department of Medicine, Division of Nephrology and General Medicine, University Hospital Freiburg, Freiburg, Germany

Abstract

Numerous acquired hemostatic abnormalities have been identified in renal insufficiency. Hemodialysis procedures add to these disturbances as they repetitively imply turbulent blood flow, high shear stress, and contact of blood to artificial surfaces. This nonphysiological environment leads to activation of platelets, leukocytes, and the coagulation cascade, resulting in fouling of the membrane and ultimately in clotting of fibers and the whole hemodialyzer. Anticoagulation in hemodialysis is targeted to prevent this activation of coagulation during the procedure. Most agents inhibit the plasmatic coagulation cascade. Still commonly used is unfractionated heparin, followed by low-molecular-weight heparin preparations with distinct advantages. Immune-mediated heparin-induced thrombocytopenia constitutes a potentially life-threatening complication of heparin therapy requiring immediate switch to nonheparin alternative anticoagulants. Danaparoid, lepirudin, and argatroban are currently being used for alternative anticoagulation, all of which possess both advantages and limitations. In the past, empirical strategies reducing or avoiding heparin were applied for patients at bleeding risk, whereas nowadays regional citrate anticoagulation is increasingly used to prevent bleeding by allowing procedures without any systemic anticoagulation. Avoidance of clotting within the whole hemodialyzer circuit is not granted. Specific knowledge of the mechanisms of coagulation, the targets of the anticoagulants in use, and their respective characteristics constitutes the basis for individualized anticoagulation aimed at achieving full patency of the circuit throughout the procedure. Patency of the circuit is an important prerequisite for optimal hemodialysis quality.

Key words: Hemodialysis, coagulation, heparins, danaparoid, argatroban, lepirudin

INTRODUCTION

Adequate anticoagulation in hemodialysis procedures relies on knowledge of the basic principles of hemostasis and notably the clotting cascade. Hemostatic abnormalities in renal insufficiency as well as activation of clotting on artificial surfaces further require attention. These aspects are discussed in the first part of this review, followed by the second part, which focuses on the principles of anticoagulation and the currently available main anticoagulants used in routine hemodialysis procedures.

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PRINCIPLES OF COAGULATION

Hemostasis can be defined as a process of fibrin clot formation to seal a site of vascular injury without resulting in total occlusion of the vessel. To this end, a complex array of multiple processes including both cellular elements and numerous plasma factors with enzymatic activity is arranged (1) to activate clotting rapidly, (2) to limit

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and subsequently terminate this activation, and (3) to remove the clot by fibrinolysis in the end.

The initial hemostatic response to stop bleeding is the formation of a platelet plug at the site of vessel wall injury. Platelets are activated by a multitude of stimuli, the most potent of which are thrombin and collagen. Upon activation, platelets adhere to the subendothelial matrix, aggregate, secrete their granule content, and expose procoagulant phospholipids such as phosphatidylserine. Platelet-derived membrane microvesicles markedly increase the phospholipid surface on which coagulation factors form multimolecular enzyme complexes with procoagulant activity. Hence, platelet activation also leads to propagation of plasmatic coagulation.

The coagulation process has long been viewed as a "cascade" of proteolytic reactions ultimately resulting in fibrin clot formation.[1,2] In this, 2 different mechanisms to initiate clotting, i.e., the extrinsic and intrinsic pathway, were defined, ultimately leading to a common pathway of coagulation. Whereas this concept fits well with the screening laboratory tests prothrombin time and activated partial thromboplastin time (aPTT), it does not sufficiently explain certain clinical observations, which challenge the view of 2 independent pathways of activation in vivo. Here, a model of cell-based hemostasis was proposed comprising of 3 overlapping stages of initiation on tissue-factor (TF)-bearing cells, amplification on platelets, and propagation on the activated platelet surface.[3,4]

For didactic purposes, the process of plasmatic fibrin generation is described based on the classical concept of a coagulation cascade, which comprises the sequential and often overlapping activation of proenzymes or zymogens to active enzymes, resulting in a stepwise amplification. Its activation occurs by initiation of the extrinsic or the intrinsic pathway (Figure 1). The *extrinsic* pathway is initiated by expression of TF, e.g., due to endothelial damage. Tissue factor is a cofactor for the production of activated factor VII (FVIIa). The TF–FVIIa complex (the extrinsic "X-ase" or tenase) activates factor X and factor IX. In vivo, clotting is primarily initiated by this TF pathway.[5] The *intrinsic* pathway, also termed the contact activation pathway, is thought to be prominently involved in activation of clotting on artificial surfaces such as hemodialysis membranes, but recent data challenge this assumption.[6] Here, contact with negatively charged surfaces leads to activation of high-molecular-weight kininogen (HMWH), prekallikrein, and factor XII in an ordered fashion (Figure 1). Activated factor XII (FXIIa) activates FXI and FXIa activates factor IX. Factor IXa and factor VIIIa form the intrinsic "X-ase" enzyme complex, which activates factor X to FXa. Therefore, the exogenous

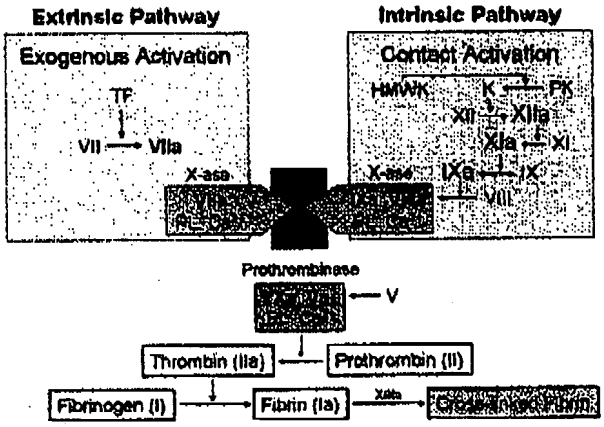

Figure 1 Plasmatic coagulation cascade. Extrinsic and intrinsic pathway of activation converge, as both result in enzyme complexes converting factor X to Xa. Factor Xa is part of the prothrombinase complex, which activates prothrombin to thrombin. Thrombin is the final key enzyme converting soluble fibrinogen to insoluble fibrin.

and contact activation pathway both converge in production of FXa, which is the central activator of the subsequent common pathway. The FXa and FVa form the prothrombinase complex, which converts prothrombin (FII) to the active protease thrombin (FIIa) with enormous efficiency. Finally, thrombin converts the soluble fibrinogen into insoluble fibrin, which is then stabilized by FXIIIa to form stable clots. Assembly and function of the aforementioned enzyme complexes require anionic phospholipid surfaces and calcium ions.

The coagulation process is terminated by the circulating enzyme inhibitors antithrombin and TF pathway inhibitor. Upon clot formation, thrombin binds to thrombomodulin. Owing to the subsequent conformational change, the substrate specificity of thrombin no longer allows for activation of platelets or cleavage of thrombin. Instead, thrombin then activates the anticoagulant protein C pathway, thus terminating its own production and activation. Concerning fibrinolysis, the reader is referred to current textbooks on hemostaseology.

HEMOSTATIC ABNORMALITIES IN RENAL INSUFFICIENCY

The accumulation of uremic toxins causes complex disturbances of the coagulation system. Uremia can lead to an increased bleeding tendency, e.g., due to platelet dysfunction,[7] which is further enhanced with use of anticoagulants during extracorporeal blood purification procedures. In contrast, clot formation and development of

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thrombosis can also occur at increased rates in dialysis patients: pulmonary embolism is more frequent in dialysis patients than in age-matched controls.[8] Patients on chronic intermittent hemodialysis frequently suffer from vascular access thrombosis,[9] the risk of which is increased in polytetrafluoroethylene grafts compared with arteriovenous fistulas.[10] Further, numerous hemostatic abnormalities have been found, which may account for the increased risk of thrombosis in end-stage renal disease (ESRD) patients, a few of which are subsequently mentioned: Patients with chronic renal failure have a high prevalence of systemic inflammation and diffuse endothelial damage that may cause hypercoagulability.[11,12] Activation of platelets and monocytes has also been detected.[13] Uremic patients with thrombotic events show significantly higher platelet-derived microparticle counts than patients without thrombotic events.[14] Antithrombin levels as well as antithrombin activity can be reduced.[15,16] In patients with ESRD, deficiencies of the anticoagulant proteins C and S have been observed.[9,15,16] Activated protein C resistance can occur[9] or activity of the anticoagulant protein C can be decreased by inhibitors.[9,17] Activation of the TF coagulation pathway has been found.[13]

These complex hemostatic abnormalities have been linked not only to thrombosis but also to progressive atherosclerosis, a frequent condition in ESRD patients.[12,15] Hypercoagulability increases as renal function declines.[12] Recently, in 16 subjects on maintenance HD, deficiencies in protein C, protein S, antithrombin, and activated protein C resistance were completely corrected within months after renal transplantation.[9] Hypercoagulability in ESRD patients therefore essentially represents an acquired and reversible condition. During the hemodialysis treatment, markers of a procoagulant state increase further despite the use of anticoagulants.[12,15,18] Although the clinical relevance of this subclinical thrombus formation is unclear, some authors suggest that an increase in heparin dose by 50% compared with standard recommendations may be warranted.[18] For further details on thrombogenesis in hemodialysis patients, the reader is referred to a recent review.[19]

ACTIVATION OF THE COAGULATION CASCADE IN THE EXTRACORPOREAL CIRCUIT

Hemodialysis causes turbulent blood flow and high shear rates.[20] Turbulent blood flow and high shear stress activate platelets directly. Shear is one major pathway of platelet-induced hemostasis and thrombosis.[21] At slow blood flow, platelets can bind to fibrinogen adherent to the artificial surface via their GPIIb/IIIa receptor. Receptor binding and thrombin formation due to contact activation result in the release of platelet secretion products, platelet aggregation, and activation of the coagulation cascade. In HD leukocytes and platelets coaggregate,[22,23] an effect that in part appears to be membrane-dependent.[24] Coaggregation is followed by activation of both cell types. On adhesion to artificial surfaces, granulocytes release the contents of their granules.[25] Granulocytes and monocytes express TF, a potent activator of the coagulation cascade.

In addition to cellular activation, contact of blood with artificial surfaces induces profound activation of plasmatic coagulation.[26] Clotting on artificial surfaces is thought to mainly occur via the intrinsic (contact activation) pathway described above. The degree to which the coagulation cascade is activated is determined by the blood flow and the local concentration of factor XIIa. In addition to the intrinsic pathway, extracorporeal blood purification procedures also activate the extrinsic (TF) pathway of coagulation.[6]

Within the extracorporeal circuit, not only the dialyzer but also other components are thrombogenic. The needles or catheters used for vascular access, the tubing, and the arterial and venous bubble traps all contribute to thrombogenesis. The arterial and venous bubble traps are very thrombogenic, because blood flow is slower and in some areas even stasis of blood may be present. In addition, the interface of air and blood and the turbulences in the bubble trap are known inductors of the coagulation cascade. Further risk factors for premature occlusion of the extracorporeal circuit are slow blood flow, high hematocrit, and blood transfusions into the extracorporeal circuit.

STANDARD ANTICOAGULATION IN HEMODIALYSIS

Routine anticoagulation for extracorporeal blood purification procedures is performed by agents interfering with the plasmatic clotting cascade. Knowledge of the specific characteristics of the agents in use is a prerequisite of adequately tailoring the anticoagulant prescription to the patient's clinical condition and the setting in which hemodialysis treatment is required.

According to their specific characteristics, anticoagulants for hemodialysis procedures can be divided into different subgroups. Here, 3 major features should be known: (1) Anticoagulants may differ by their chemical composition. For example, heparins and danaparoid are glycosaminoglycans, the direct thrombin inhibitor lepirudin is a large polypeptide, and the small direct thrombin

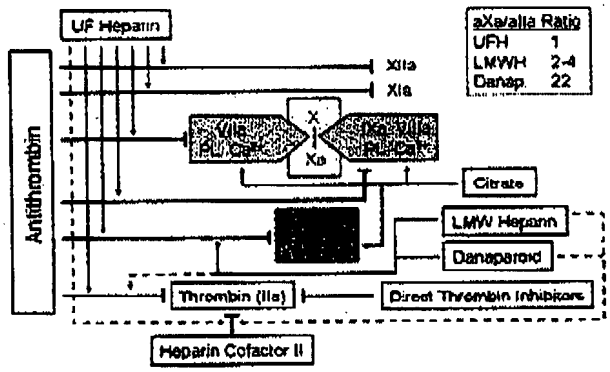

Figure 2 Targets of selected anticoagulants within the coagulation cascade. Antithrombin and heparin cofactor II inhibit key factors in the clotting cascade. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and danaparoid are indirect agents increasing the activity of the natural inhibitors. Direct thrombin inhibitors block thrombin. Citrate chelates calcium and thereby inhibits all steps of the coagulation cascade.

inhibitor argatroban is a synthetic derivative of arginin. (2) Anticoagulants may exert their inhibition of the clotting cascade indirectly by binding to physiological anticoagulants. This is the case for the heparins and danaparoid, whose action mainly depends on the presence of antithrombin. In contrast, the direct thrombin inhibitors do not require natural cofactors for their action. (3) Anticoagulants may differ in their targets within the clotting cascade or may exert different inhibitory potency for the same target. For example, by definition, unfractionated heparin (UFH) inhibits FXa and FIIa with equal potency, whereas danaparoid predominantly inhibits FXa. Figure 2 depicts the targets of selected anticoagulants within the clotting cascade.

The subsequent sections can only give a short overview on each anticoagulant agent or strategy. The information provided therein does not allow for proper use of the respective anticoagulant. Careful evaluation of the information provided by the manufacturer and the dose recommendations given is a prerequisite for their use. For further details on anticoagulation for hemodialysis procedures, the reader is referred to an overview published recently.[19]

Unfractionated heparin

Unfractionated heparin preparations constitute a mixture of anionic glucosaminoglycans of varying molecular size (5–40, mean 15 kDa). The main action of heparin on the coagulation system is indirect due to the binding to antithrombin ("heparin-binding factor I"). Heparin enhances the activity of this natural anticoagulant protein 1000 to 4000-fold. Antithrombin inactivates thrombin, factor Xa, and to a lesser extent factors IXa, XIa, and XIIa. At high doses, heparin also binds to "heparin-binding factor II." Heparin is ineffective against thrombin or factor Xa if they are located in a thrombus or bound to fibrin or to activated platelets. Because UFH has a narrow therapeutic window of adequate anticoagulation without bleeding, laboratory testing (aPTT or as bedside test "activated clotting time," ACT) of its effect is required. In addition to increasing the bleeding risk, other side effects of heparin are worsening of osteoporosis and lipid status, allergic reactions such as pruritus, and thrombocytopenia. Immune-mediated heparin-induced thrombocytopenia (HIT) is a rare but life-threatening complication of heparin therapy.[27,28]

Application of heparin during hemodialysis requires an initial loading dose, followed by a maintenance dose: as an initial loading dose, the European best-practice guidelines for HD recommend administering 50 IU/kg UFH into the arterial access needle.[29] The maintenance dose of heparin is 500 to 1500 IU of UFH/hr, given via constant infusion into the arterial line using an infusion pump.[29] Alternatively, the maintenance dose can be given as repeated bolus injection. During intermittent HD, the patient is systemically anticoagulated. The ACT is adjusted to 80% above the baseline value. Because the hemodialysis patient is systemically anticoagulated for at least 4 hr, aPTT should be checked before surgical procedures after dialysis. Heparin requirements during HD are determined by patient-related factors, the amount of heparin adsorption to the membrane of the dialyzer, and the thrombogenicity of components of the extracorporeal circuit.

Table 1 lists the dose recommendations for use of UFH for intermittent HD. The recommendations should be considered as guidelines and not followed uncritically in any individual patient.

Low-molecular-weight heparin (LMWH)

Low-molecular-weight heparin preparations comprise a mixture of anionic glucosaminoglycans with a smaller size (molecular weight: 4–8 kDa) compared with UFH. The LMWH also bind to antithrombin. However, because of the short chain length of LMWH, antithrombin/LMWH complexes have less affinity to thrombin, resulting in a reduced inhibition of thrombin compared with UFH. The inhibitory effect on factor Xa vs. thrombin is 1:1 for UFH but 2.5:1 or 3:1 in LMWH, depending on the individual

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Table 1 Anticoagulation during intermittent hemodialysis

	Indication	Dose	Comment
Unfractionated heparin (UFH)			
Standard heparin	Patient with normal bleeding risk	Initial loading: 50 IU/kg MD: 500 to 1500 IU/hr	Target ACT: 80% above baseline, depending on dialyzer used
Low heparin (with maintenance dose)	Patient with increased bleeding risk	Initial loading 10 to 25 IU/kg MD: 250 to 500 IU/hr	Target ACT: 40% above baseline in venous line
Very low heparin (without loading or maintenance dose)	Patient with very high bleeding risk or active bleeding	Rinse dialyzer with 5000 to 20,000 IU of heparin, flush system with 0.5 to 2 L of saline. Intermittently rinse with normal saline.	Target ACT: no change from baseline. Keep blood flow $\geq$ 250 mL/min
Low-molecular-weight heparin (LMWH)			
	Improvement of lipids possibly: less osteoporosis, less pruritus, less hair loss, less blood transfusions compared with UFH		Monitoring requires measurement of anti-factor Xa-activity in venous line (aPTT and ACT are unreliable)
Dosing of selected drugs (according to the manufacturers' information)			
Dalteparin		*In patients with a low bleeding risk:* either 85 anti-Xa-IU/kg as bolus (HD up to 5 hr) or initial bolus 30 to 35 IU/kg; MD: 10 to 15 IU/kg/hr (target anti-Xa-level: $\geq$ 0.5 IU/mL) *In patient with a high bleeding risk:* initial bolus 5 to 10 IU/kg; MD: 4 to 5 IU/kg/hr (target anti-Xa-level: 0.2 to 0.3 max. 0.4 IU/mL)	
Enoxaparin		100 anti-Xa-IU/kg as single bolus (if clots are formed: repeat 50 to 100 anti-Xa-IU/kg) *In patients with a high bleeding risk:* 50 anti-Xa-IU/kg with use of double lumen catheter 75 anti-Xa-IU/kg with use of single lumen catheter	
Nadroparin		*With a normal bleeding risk and dialysis up to 4 hr:* <50 kg, 2850 anti-Xa-IU as single bolus 50 to 69 kg, 3800 anti-Xa-IU as single bolus > 70 kg, 5700 anti-Xa-IU as single bolus	
Tinzaparin		4500 IU as single bolus into arterial line increase by 500 IU for next HD, if clots visible; decrease by 500 IU for next HD, if prolonged bleeding after HD at arterio-venous fistula	

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Heparinoid substance				
Danaparoid	In HIT type II	Rinse system with 750 IU		
		Bolus weight adjusted	< 55 kg	> 55 kg
		Before 1st HD	2500 IU	3750 IU
		Before 2nd HD	2000 IU	3750 IU
		Before 3rd and following HD treatments: measure anti-factor Xa-level; target in venous line: up to 0.5 to 0.8 IU/mL, adjust dose accordingly:		
		anti-Xa < 0.3:	2000 IU	3000 IU
		anti-Xa 0.3 to 0.35:	2000 IU	2500 IU
		anti-Xa > 0.35	1500 IU	2000 IU
Direct thrombin inhibitors				
Hirudin				
Lepirudin	In HIT type II	Dose applies to high-flux-dialyzer: 1st HD: bolus: 0.1 mg/kg; for subsequent HDs dose depends on aPTT before HD: bolus: 0.05 to 0.1 mg/kg	High risk of bleeding complications; no antidote available; target hirudin levels: 0.5 to 0.8 µg/mL target aPTT 50 to 75 s	
Argatroban	In HIT type II	250 µg/kg loading dose before HD MD: 1.7 to 3.3 µg/kg × min (in normal liver function)	Target aPTT: 1.5 to 3 × mean of normal range	
Citrate	In patients with high bleeding risk	3 mmol citrate/L blood flow (e.g., 50 mmol/hr at a blood flow of 250 mL/min) Ca^{2+}-infusion: blood flow into venous line	Target ACT: 200 to 250 s in venous line use no calcium and low sodium in dialysate adjust according to target > 1 mmol/L ionized Ca^{2+} in arterial line	

ACT = activated clotting time; aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; MD = maintenance dose.

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LMWH preparation. Several LMWH preparations have been marketed, which differ in their chemical and pharmacokinetic properties. Despite not being interchangeable, LMWH preparations share the following common features: (1) The anticoagulant effect (anti-Xa activity) of LMWH in patients with normal renal function is highly correlated with body weight, allowing use of a fixed dose per kilogram body weight. Laboratory monitoring is not necessary in patients with normal renal function. (2) In renal failure, dosing has to be reduced. (3) If monitoring is performed, anti-factor Xa activity needs to be measured, while aPTT and ACT are not reliable.[30,31] Recently, a modified Xa-ACT has been demonstrated to measure reliably the anticoagulant effect of LMWH preparations within a point-of-care setup.[31] If anti-factor Xa activity is measured, a level of >0.5 IU/mL is recommended in the venous line of the extracorporeal circulation. In patients at high risk of bleeding, a lower anti-Xa activity may be sufficient to prevent clotting of the dialysis circuit. (4) LMWH are much less likely to induce HIT type II. A more detailed description of common features of LMWH has been given elsewhere.[19]

Table 1 lists dose recommendations for use of LMWH for intermittent HD as provided by the manufacturers. The recommendations should be considered as guidelines and not followed uncritically in any individual patient.

ALTERNATIVE ANTICOAGULATION IN HIT

A moderate decline in platelet count is frequently observed after commencing HD. However, thrombocytopenia during heparin therapy may hint at immune-mediated HIT, which constitutes a potentially life-threatening complication. This requires immediate diagnostic and appropriate therapeutic measures.[27,28]

Heparin-induced thrombocytopenia type I

Within the first 2 to 3 days of heparin therapy, a modest reduction in platelet count ($<100,000$/mL) is frequently seen. This is not due to an immunologic reaction but is caused by a direct heparin-induced degranulation of platelets. This type of thrombocytopenia (HIT type I) is regarded as harmless. Platelet count increases even though heparin therapy is continued.

Heparin-induced thrombocytopenia type II

From 4 to 10 days after initiating heparin therapy, HIT type II may develop, which is an immune-mediated disease (now commonly referred to as "HIT" and likewise in the consecutive sections in this review). Antibody formation against the complex of heparin and platelet factor 4 ("HIT antibodies") is the cause of this devastating disease. If HIT is suspected, immediate action has to be taken and all heparin application has to be stopped, even before laboratory test results are available confirming the presence of antibodies. Occasionally, HIT manifests immediately on start of heparin therapy, if the patient had previous contact with heparin. In HIT, thrombocytopenia ($>20,000$/mL, mean 60,000/mL) indicates platelet consumption owing to the disease process. Here, low platelet count is not associated with bleeding complications; instead, venous and arterial thromboembolism may occur. Among the procoagulant abnormalities of the coagulation system, HIT presents with the highest rate of clot formation (50% within 30 days).[32] HIT is also called the "white clot syndrome," because characteristic platelet-rich, white arterial thrombi are formed. These may manifest in a dramatic clinical picture with ischemia of one or several limbs and a high mortality rate due to cerebral or myocardial infarctions. However, the majority of thrombi are formed in the venous system including the lungs. The venous manifestations are frequently overlooked or not interpreted as a manifestation of HIT.

Anticoagulation in hemodialysis patients with HIT

If HIT is likely to be present, all applications of heparin have to be stopped, including heparin ointments to the skin or heparin-coated catheters. A "heparin-free dialysis" must not use heparin for initial rinsing. LMWH preparations must also be avoided. Although LMWH induce HIT antibodies less frequently than UFH, they have a high rate of cross-reactivity once UFH has induced HIT antibody formation. As long as the platelet count is low in active HIT, systemic anticoagulation is mandatory to reduce the risk of life-threatening thrombus formation. During this time, it is not sufficient to use, e.g., regional citrate anticoagulation that merely prevents clot formation in the extracorporeal circulation. Established systemic alternative anticoagulation in patients with HIT is performed with danaparoid, lepirudin, or argatroban. Additionally, fondaparinux may become an additional alternative option.

The subsequent sections only can give a short overview on each anticoagulant agent. The information provided therein does not allow for proper use of the respective anticoagulant. Careful evaluation of the information provided by the manufacturer and the dose recommendations

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given is a prerequisite for their use. For further details on alternative anticoagulation for hemodialysis procedures in HIT patients including the numerous caveats, the reader is referred to a detailed review published recently.[28]

Danaparoid

Danaparoid is a heparinoid of low molecular weight (5.5 kDa) consisting of heparan sulfate (83%), dermatan sulfate, and chondroitin sulfate. Danaparoid constitutes the alternative anticoagulant that was most widely used for management of HD in patients with HIT.[33] In 2002, danaparoid was withdrawn by the manufacturer from the U.S. market, whereas it is still available in Canada and the European Community.

The main anticoagulant effect of danaparoid depends on binding to antithrombin and heparin cofactor II. Factor Xa is more selectively inhibited than with the use of LMWH. The activity ratio for factor Xa to thrombin inhibition is 22:1 (compared with 3:1 with LMWH). Danaparoid has a low rate of cross-reactivity against HIT antibodies. During danaparoid treatment, HIT antibodies can be detected in vitro in 10% of cases. In 6.5% of patients with HIT, persistent or repeated thrombocytopenia was observed with use of danaparoid.[34] As positive in vitro cross-reactivity is of uncertain clinical significance, attention should focus on platelet count monitoring after starting danaparoid application. A further decline in platelet count, or new fibrin deposits and clot formation within the extracorporeal circuit after application of danaparoid, may indicate clinically relevant cross-reactivity. For monitoring of danaparoid therapy anti-Xa activity has to be measured, and aPTT is not helpful. The half-life of the anti-Xa activity of danaparoid is 25 hr in patients with normal renal function and is further prolonged in uremia. An antidote is not available.

Table 1 lists the dose recommendations for use of danaparoid for intermittent HD as provided by the manufacturer. The recommendations should be considered as guidelines and not followed uncritically in any individual patient. If applied with appropriate care, danaparoid provides adequate anticoagulation for HD of HIT patients with a favorable benefit/risk ratio, even during long-term use. Before invasive procedures, appropriate (repetitive) laboratory measurements have to be carried out in hemodialysis patients on danaparoid treatment.

Direct thrombin inhibitors

Direct thrombin inhibitors do not require natural cofactors to inhibit the clotting cascade. Instead, they directly bind to and block thrombin, the final key enzyme within the coagulation process inducing the conversion of soluble fibrinogen to insoluble fibrin. From the different thrombin inhibitors currently available, lepirudin and argatroban are approved for alternative anticoagulation in HIT (in the United States and a number of other countries).

Hirudin

Lepirudin is a recombinant hirudin preparation approved for the treatment of HIT in patients. Lepirudin is difficult to use in patients with renal failure or on dialysis.[35,36] Because it is mainly eliminated by the kidneys, its half-life is markedly prolonged in renal failure.[37] After a single loading dose, the patient may be therapeutically anticoagulated for 1 week or longer. Therefore, bleeding risk is increased especially when interventions or surgery cannot be circumvented. In this regard, adequate hirudin dosing is essential.[35] Hirudin dose requirements in critically ill patients on continuous HD are minimal, especially in the case of anuria.[38] Bleeding risk can be reduced by applying hirudin as a bolus rather than continuous infusion. In case of bleeding complications, there is no antidote available to antagonize the anticoagulant effect of hirudin. High-volume hemofiltration, but not HD, is effective in reducing hirudin plasma levels.[39,40] An ultrafiltrate volume of 15% of body weight reduces hirudin plasma levels by 50%.[39]

Hirudin constitutes a polypeptide and does not show cross-reactivity to HIT antibodies. Yet, up to 74% of patients treated with hirudin for more than 5 days develop anti-hirudin antibodies (aHAb).[41,42] The presence of aHAb often requires dose adjustments.[41,43] Recent in vivo studies clearly show that hirudin action is markedly prolonged because aHAb delay its renal clearance even without renal impairment.[44] In the presence of aHAb, hemofiltration no longer constitutes a rescue measure to reduce hirudin plasma levels rapidly.[44] This aim may be achieved only by plasmapheresis.

Monitoring of therapy is frequently performed by measuring aPTT (target range 1.5–2.5 of normal). Activated partial thromboplastin time is not ideal for monitoring lepirudin therapy, because it does not linearly increase with lepirudin blood levels and effect; thus, high aPTT levels may correspond to very high lepirudin levels.[45] Lepirudin levels are more reliably assessed by ecarin clotting time or chromogenic substrate assays.[45]

Table 1 lists the dosing recommendations for use of lepirudin for intermittent HD. The recommendations should be considered as guidelines and not followed

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uncritically in any individual patient. Hirudin is a valid alternative anticoagulant for HD procedures in HIT patients, but it should be used with caution and careful monitoring. Especially before invasive procedures, appropriate (repetitive) laboratory measurements have to be carried out in hemodialysis patients on lepirudin treatment.

Argatroban

Argatroban is a potent arginine-derived, synthetic, catalytic site-directed thrombin inhibitor being approved as an alternative anticoagulant for HIT in the United States, Canada, and a number of European countries. It does not cross-react with HIT antibodies. In contrast to hirudin, argatroban is metabolized primarily by the liver, and its half-life is only moderately extended in patients with renal insufficiency.[46]

In a retrospective analysis of 47 HIT patients requiring renal replacement therapy, argatroban provided effective anticoagulation with an acceptable safety profile.[47] A prospective cross-over study of 12 maintenance HD patients showed different argatroban dosing regimens to be safe and well tolerated.[48]

There are conflicting data concerning the necessity of dose adjustments of argatroban in renal failure.[49–51] In ICU patients suffering from overt renal and additionally from occult liver insufficiency, dose reductions may be frequently necessary (unpublished observations of the author). Based on this experience, in ICU patients, in our center we start argatroban at a reduced dose, provided there is no acute thrombosis. Careful monitoring and dosing is required. Similar experiences have also been reported by others.[50] Periodic monitoring of the anticoagulant activity of argatroban is recommended using for example the aPTT, the ECT, or the activated clotting time (ACT).[48,49]

Argatroban appears to be at least as well suited as lepirudin for anticoagulation of HIT patients requiring HD. Its predominant hepatic elimination favors argatroban for alternative anticoagulation in chronic renal failure. Its role and dosing in ICU patients suffering from acute renal failure remain to be defined.

Table 1 lists the dosing recommendations for use of argatroban for HD. The recommendations should be considered as guidelines and not followed uncritically in any individual patient. In particular, ICU patients often do not require full-dose argatroban. Before invasive procedures, appropriate (repetitive) laboratory measurements have to be carried out in hemodialysis patients on argatroban treatment.

Other agents–fondaparinux

Fondaparinux is a fully synthetic pentasaccharide derived from the minimal binding region of heparin to the antithrombin molecule and exerts high anti-Xa activity.[52] Despite not being formally approved, fondaparinux has occasionally been used for alternative anticoagulation in HIT patients. The half-life is longer than with LMWH preparations and is further prolonged in renal failure. Therefore, its dose is to be reduced for anticoagulation in patients with renal insufficiency and for HD procedures. Recently, successful anticoagulation with fondaparinux has been described in a maintenance HD patient with symptomatic HIT.[53] The role of fondaparinux for anticoagulation in HD procedures of HIT patients requires further evaluation.

Role of regional citrate anticoagulation in HIT

Regional citrate anticoagulation (for details see below) allows the use of heparin-free HD without systemic anticoagulation. As long as platelet count is decreased in HIT or other laboratory or clinical signs of active disease with thromboembolism are present, extracorporeal anticoagulation alone is insufficient and systemic anticoagulation using hirudin, danaparoid, or argatroban is mandatory. If systemic anticoagulation is no longer indicated, but repeated heparin use should be avoided for a prolonged period of time, regional citrate anticoagulation is an excellent choice to prevent recurrence of HIT.

Alternative anticoagulation in HIT

Low-dose UFH

Even in patients at high risk for bleeding complications, UFH still is the most frequently used agent for anticoagulation during HD, although at a reduced dose. In "low heparin" intermittent HD, the system is rinsed with 2500 to 5000 IU of heparin and subsequently with at least 2 L saline solution to remove the anticoagulant that has not bound to the surface of the artificial polymers. The following hemodialysis treatment uses a low-maintenance dose of heparin in order to maintain the systemic ACT no higher than 40% above baseline.

Heparin-"free" hemodialysis

If the bleeding risk is extremely high (e.g., in patients at risk for intracranial bleeding), maintenance heparin is completely avoided. This is possible if dialysis

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membranes with low thrombogenicity (e.g., polysulfone), a short treatment time (2–3 hr), and a high blood flow (> 250 mL/min) are used. It may be helpful to rinse the extracorporeal system repeatedly with saline (25–150 mL injected into the arterial line every 15–30 min). This treatment without maintenance dosing is frequently called "heparin-free dialysis." However, with commencement of the treatment the patient receives a small dose of heparin as the extracorporeal circuit is connected to the patient's circulation. In addition, during the treatment, adsorbed heparin can be released from the artificial polymers and reach the patient. The amount of heparin is very low and does not elevate aPTT or ACT. However, if the patient has developed HIT antibodies even a small amount of the substance is sufficient to trigger the immunologic process again. Therefore, in case of HIT the so-called "heparin-free dialysis" (applying heparin for recirculation into the tubing system, followed by saline washout) must not be used. Even heparin-coated catheters or dialyzers are not allowed.

Regional citrate anticoagulation

Regional citrate anticoagulation is an interesting alternative method compared with heparin in patients with a high bleeding risk. Citrate infused into the arterial line chelates calcium and magnesium, and thus inhibits the coagulation cascade in the extracorporeal circulation. The deficit in ionized calcium is present only locally in the extracorporeal circulation because, before blood reinfusion, calcium is substituted into the venous line to target normal ionized calcium. Some aspects of citrate anticoagulation necessitate a modification of the dialysis prescription: (1) Citrate is metabolized in the liver to form bicarbonate, and may induce metabolic alkalosis. To compensate for this bicarbonate production, bicarbonate concentration in the dialysate needs to be reduced to avoid metabolic alkalosis. (2) Trisodium citrate may induce hypernatremia. To compensate for sodium infusion, the sodium concentration in the dialysate should be reduced. (3) Dependent on the respective ionized calcium concentration, both the citrate and calcium infusion are to be modified: (a) If in the venous line (before calcium substitution) the concentration of ionized calcium is not low enough, or ACT is too short, the citrate infusion rate should be increased. (b) If ionized calcium in the arterial line (before citrate infusion) is too low, calcium infusion has to be increased to avoid systemic hypocalcemia.

Development of alkalosis is usually not a problem in intermittent HD, as citrate anticoagulation is used for only a few hours per week. In addition, many of the citrate calcium complexes are removed into the dialysate and are not infused into the patient.

It has been demonstrated that bleeding complications are reduced compared with low-dose heparin.[53] Citrate anticoagulation also improves biocompatibility and reduces deposition of blood components on the dialysis membrane compared with UFH or LMWH.[54,55] A simplified treatment protocol has recently been published and may help to promote this valuable option in HD therapy.[56]

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